REMARKS

Claims 1-4, 6-18, 19, 20, 21, 34-38, 40-46 and 56-59 are pending. Claims 19, 34 and 47-55 are withdrawn from consideration, and the remaining pending claims are rejected. Applicants herein cancel claims 11 and 38 without prejudice and purely in the interest of advancing prosecution. Upon entry of the instant Amendment, claims 1-4, 6-10, 12-18, 19, 20, 21, 34-37, 40-46 and 56-59 will be pending.

Rejection under 35 U.S.C. 112

The Examiner rejects claims 11 and 38 as allegedly unclear since lamellar bodies are by definition made in a lab (synthetic). Applicants herein cancel these two claims without prejudice thereby obviating the rejection.

Rejection under 35 U.S.C. 103

1. WO 91/12026 in view of Szoka, U.S. Patent 5,077,057 further in view of Sheffield *et al.*, U.S. Patent 4,937,254

The Examiner rejects claims 1-4, 6-18, 20-21, 35-38, 40-46 and 56-59 as allegedly unpatentable over WO 91/12026 in view of Szoka, U.S. Patent 5,077,057 further in view of Sheffield *et al.*, U.S. Patent 4,937,254. According to the Examiner, WO 91/12026 teaches reducing surgical adhesions by coating tissue surfaces with phospholipids, including less pure phospholipids, in combination with hyaluronic acid. The Examiner says that it is obvious that this is a lamellar composition. The Examiner admits that WO 91/12026 does not teach the amounts of each phospholipid in the mixture but says that it would be obvious to optimize the relative amounts of each. Further, it would allegedly be obvious to use commercial lecithin in combination with the other phospholipids. In addition, the Examiner says the number of liposomes and administration protocol would be obvious absent evidence of unexpectedly superior results.

The Examiner says that Szoka teaches including cholesterol in liposomes to increase rigidity and encapsulating chemotherapeutic agents. Hence, it would allegedly be obvious to add cholesterol to the present compositions as well as chemotherapeutic agents. The Examiner says that Sheffield *et al.* teach inhibiting post surgical adhesion by topically administering liposomes containing phosphatidylcholine and cholesterol in combination with hyaluronic acid. According to the Examiner, it would be obvious that the preparations of WO 91/12026 would be in the form of liposomes since Sheffield *et al.* teach liposomes are formed by adding an aqueous medium to phospholipids.

The Examiner was not persuaded by the explanations and arguments that Applicants presented in the Amendment and Response last January. The Examiner contends that the term "lamellar bodies or microbodies" as used in the specification refers to both synthetic and naturally occurring and synthetic lamellar bodies.

a. The prior art does not teach or suggest the presently claimed compositions

Applicants respectfully traverse. WO91/12026 teaches a method for the reduction or prevention of unwanted surgical adhesions between two tissue surfaces which comprises interposing between said surfaces an effective amount of 'a' phospholipid in suspension or solution. The primary teaching is that 'the' phospholipid of interest is phosphatidylcholine (or lecithin). WO91/12026 teaches that the purity of the phospholipid is normally 99% (see page 5 of WO91/12026). While WO91/12026 does allow for mixtures or combinations of phospholipids, there is no specific teaching of combining phospholipids as claimed by the present application. Furthermore, the number of possible combinations of phospholipids is vast, even from the list provided by Table 1 of WO91/12026.

(i) Regarding ratios

WO91/12026 teaches that the phospholipid (phospatidylcholine) is preferably 99% pure and also teaches that the phospholipids, phosphatidylinositols, phosphatidylserines, phosphatidylglycerides and sphingomyelin are present as impurities, although the impurities may act synergistically. WO91/12026 therefore teaches against a phospholipid mixture and in particular against a phosphatidycholine mixture containing phosphatidylinositols, phosphatidylserines and sphingomyelin. Even if, *assuming arguendo*, WO91/12026 did suggest using each of the listed impurities in combination, one of ordinary skill in the art would consider from the phrase "The levels of these impurities should preferably be kept below 0.1% (see page

6 lines 3 to 4)" that any impurities present in the phospholipid are present in small amounts. The Examiner submits that one of ordinary skill in the art would be motivated to use commercial lecithin in combination with other phospholipids with a reasonable expectation of success. Applicants respectfully disagree. Rather, Applicants submit that in view of the teaching of WO91/12026 to provide a phospholipid, preferably 99% pure phosphotidylcholine, one of ordinary skill in the art would be dissuaded from providing the composition as presently claimed which requires phosphotidylcholine to be present at 44-60% and in combination proportions of other phospholipids such as 15-23% sphingomyelin and 6-10% phosphatidylethanolamine. Applicants submit that the prior art does not teach or suggest these proportions. Therefore, these proportions are significant and innovative.

Applicants reiterate that even if, *assuming arguendo*, the particular combination of phospholipids as presently claimed could be said to be suggested by the prior art, WO91/12026 teaches against providing ratios of such phospholipids greater than 0.1%. As such, in view of the possible ratios of phospholipids which could be provided, the ratios according to the present invention are neither taught by or suggested by the prior art.

(ii) Regarding cholesterol

The compositions of the instant invention also comprise cholesterol. WO91/12026 does not teach or suggest adding cholesterol. The Examiner indicates that Szoka teaches that including cholesterol in liposomes increases the rigidity of the liposomes and further teaches the encapsulation of chemotherapeutic agents. However, Applicants do not maintain that the main aim of the synthetic lamellar body-like product is to encapsulate therapeutic agents. Importantly, liposomes are carriers for therapeutic agents, as is clear from Szoka. In the present invention, the lamellar body composition itself, having a very specific composition as described above, provides unexpected and beneficial properties of modifying fibrin deposition. The lamellar body-like composition of the present invention, by virtue of its surface charge, attracts oppositely charged molecules including therapeutic agents and so also act as a carrier. Therefore, the inherent properties of the lamellar body-like composition according to the instant invention, which are provided as a result of the specific proportions of constituents, both clearly differentiate the presently claimed compositions from the liposome compositions of the prior art and provide unexpected advantages over the liposome compositions of the prior art.

Including cholesterol in the the lamellar body-type composition according to the instant invention is important. However, unlike like the liposome compositions described by Szoka, the present invention does not require a rigid carrier where the aim is simply to encapsulate a therapeutic substance. On the contrary, the lamellar body-like composition of the present invention is a vesicle with a level of fluidity due to the low proportion of cholesterol. The Examiner maintains that "the inclusion of cholesterol would have been obvious to one of ordinary skill in the art since the inclusion of cholesterol would rigidify the membranes of liposomes." Applicants respectfully submit that since cholesterol would rigidify the membranes, the prior art actually teaches away from the specific composition according to the present invention. An object of the present invention is not to obtain a rigid liposome, but to retain a level of fluidity thereby allowing the lamellar body-like structure to permeate and disaggregate fibrin and prevent adhesions. Generally it is accepted that when including cholesterol into a liposome those skilled in the art would incorporate greater than 20% in order to increase rigidity to an extent that would improve encapsulation. (*See*, New RRC. Preparation of liposomes. In: Liposomes: A practical approach. New RRC (ed). Oxford Univ Press. 1997; 2: 33-103.) The present invention provides a ratio of 4-12% cholesterol. This represents an amount that is neither taught nor suggested by the prior art.

The Examiner states that Sheffield *et al.* teach a method of inhibiting post-surgical adhesions by administering liposomes. Applicants submit that Sheffield *et al.* teach a liposome containing or encapsulating a non-steroidal anti-inflammatory drug. Sheffield *et al.* do not teach or suggest that a phospholipid vesicle could itself have therapeutic benefit (in fact it would not as it does not comprise the necessary components in the necessary ratios) without the presence of an encapsulated active drug. The present invention provides a specific lamellar body-like product, that itself acts to permeate and disaggregate fibrin, the major macromolecule constructs that cause adhesions between tissue surfaces. One of ordinary skill in the art would find no motivation to combine the teachings of Sheffield *et al.* with the teachings of WO91/12026 as in Sheffield *et al.* the liposome is an inert carrier rather than an active therapeutic substance in its own right. Applicants submit that Sheffield *et al.* teach using a non-steroidal anti-inflammatory drug to treat surgical adhesions, and the phospholipid vesicles discussed therein are merely provided to encapsulate the drug.

b. The presently claimed compositions provide unexpectedly superior results.

It is a fundamental principle of the patent law that what might be otherwise unpatentable under 35 U.S.C. 103, may be rendered patentable if it provides unexpectedly superior properties or results. The innovation of the synthetic lamellar body composition penetrating and permeating fibrin gel, the precursor to adhesions is described in the present application. The innovation of the lamellar bodies composition over other phospholipids and phospholipid mixtures is supported by experimental data comparing the effect of the synthetic lamellar body (LMS-611) to other phospholipid mixtures, liposomes and surfactants (submitted herewith as Appendix 1). These data demonstrate that the synthetic lamellar body LMS-611, having the specific ratio of constituents as recited in the present claims, is significantly more potent than other phospholipid mixtures tested (such a phiosphotidylcholine according to WO91/12026). As the effect of phospholipids on biological gels is biophysical in nature, these data can be correlated with the effect of phospholipid mixtures on fibrin and adhesions when the synthetic lamellar body composition stands out as a significant innovation.

2. Sheffield *et al.*, U.S. Patent 4,937,254 in view of WO 91/12026

The Examiner rejects claims 1-4, 6-18, 20-21, 35-38, 40-46 and 56-59 as allegedly unpatentable over Sheffield *et al.*, U.S. Patent 4,937,254 in view of WO 91/12026. The Examiner admits that Sheffield *et al.* do not teach using phosphatidylethnolamine, phosphatidyl inositol, phosphatidylserine, phosphatidyl glycerides and sphingomyelin in liposomes. However, the Examiner says that including the claimed phospholipids would have been obvious since WO 91/12026 teaches that the combination of phospholipids act synergistically.

Again, the Examiner was not persuaded by the explanations and arguments that Applicants presented in the Amendment and Response filed last January. The Examiner contends that the term "lamellar bodies" or "microbodies" as used in the specification refers to both synthetic and naturally occurring and synthetic lamellar bodies.

The Examiner submits that there is a method of inhibiting post surgical adhesions by the topical administration of liposomes. However, as stated above, Applicants submit that Sheffield *et al.* teach liposomes that are simply carriers for an active non-steroidal anti-inflammatory drug, and it is the drug which has the therapeutic effect. Notably, in the present invention, in order for the claimed lamellar body-like product to itself have effect, it must have the claimed composition with constituents in the appropriate amounts. Sheffield *et al.* teach a method of inhibiting post surgical adhesions by administering non-steroidal anti-inflammatory drugs that are carried by a liposome to the site of interest. The liposome formulations described by Sheffield *et al.* are not similar to the composition as presently claimed and would not be effective alone because of this. Indeed, Sheffield *et al.* teach, for example at column 6 lines 37 to 44, against the compositions presently claimed. Sheffield *et al.* clearly teach that it is preferred to use "pure or synthetic phosphatidylcholine in which the fatty acid moieties in the phosphatidylcholine molecule are derived from a single fatty acid in preparing the vesicle instead of natural lecithin, which is ordinarily a mixture of compounds." Thus, if the teachings of WO91/12026 and Sheffield *et al.* are combined, in view of the teaching of both documents to use "pure" phosphatidylcholine, the present compositions are not provided. Likewise, the present compositions are not suggested. Combining both documents would thus simply result in the phospholipid of Sheffield *et al.* being applied along with a non-steroidal anti-inflammatory drug and would not lead to the specific composition of the present invention which is particularly effective in preventing fibrin deposition.

3. Sheffield *et al.*, U.S. Patent 4,937,254 in view of WO 91/12026 further in view of Vournakis, U.S. Patent 5,624,679

The Examiner rejects claims 16-18, 31-33, and 44-46 as allegedly unpatentable over Sheffield *et al.*, U.S. Patent 4,937,254 in view of WO 91/12026 further in view of Vournakis, U.S. Patent 5,624,679. According to the Examiner, Vournakis teaches that chemotherapeutic agents and anti-estrogens (tamoxifen) may be included in anti-adhesion (poly-acetylgalactosamine) compositions. Hence, the Examiner says that combining these agents would have been obvious. Again, the Examiner was not persuaded by Applicants' explanations and arguments. Rather, the Examiner contends that Shefffield teaches lamellar bodies.

Applicants submit that the important difference between the current invention and the cited prior art is that, although the compositions of the current invention can carry anti-estrogens and chemotherapeutic agents, they also have therapeutic properties in their own right and do not simply act as a carrier. Therefore, by using the specific composition of the current invention, unexpectedly beneficial effects on fibrin modification are observed. These unexpectedly beneficial effects may act in synergy or in parallel with other active substances that are being delivered. Vournakis and Sheffield *et al.* both teach compositions with no claim that the carrier is itself therapeutically active. In fact the compositions of the prior art would not be therapeutically active as they do not comprise the correct components in the required ratios.

Applicants submits that neither Sheffield *et al.* nor WO91/12026, alone or in combination with any of the other cited documents, teach or suggest the lamellar body-like composition having a specific combination and specific ratio of phospholipids and cholesterol according to the present invention. Moreover, the prior art teaches away from the specific mixture of phospholipids and other components of the instant invention that produce a lamellar body-like structure having unexpectedly superior and beneficial effects that may be used in treating or preventing surgical adhesions. None of the other cited prior art describes phospholipid vesicles that themselves have therapeutic benefit. Rather, the compositions of the prior art simply act as carriers for other active drugs.

4. WO 91/12026 in view of Szoka, U.S. Patent 5,077,057 optionally in view of Sheffield *et al.*, U.S. Patent 4,937,254 further in view of Vournakis, U.S. Patent 5,624,679

The Examiner rejects claims 16-18, 31-33, and 44-46 as allegedly unpatentable over WO 91/12026 in view of Szoka, U.S. Patent 5,077,057 optionally in view of Sheffield *et al.*, U.S. Patent 4,937,254 further in view of Vournakis, U.S. Patent 5,624,679. Basically, the Examiner says that combining chemotherapeutic and anti-estrogens with the agents for anti-adhesion would have been obvious. Applicants reiterate that WO91/12026, alone or in combination with any of the other cited documents, does not teach or suggest the lamellar body-like composition having a specific combination and specific ratio of phospholipids and cholesterol according to the present invention. Moreover, the prior art teaches away from the specific mixture of phospholipids and other components of the instant invention that produce a lamellar body-like structure having unexpectedly superior and beneficial effects that may be used in treating or preventing surgical adhesions. None of the other cited prior art describes phospholipid vesicles that themselves have therapeutic benefit. Rather, the compositions of the prior art simply act as carriers for other active drugs.

Rejection under the judicially created doctrine of obviousness type double patenting

The Examiner rejects claims 1-4, 6-18, 20-21, 35-38, 40-46 and 56-59 as allegedly provisionally unpatentable as obvious over copending claims 1-15 of United States Serial No. 10/827,172. Applicants submit their willingness to file a Terminal Disclaimer upon notification of allowable subject matter.

FEES

No additional fees are believed necessary in connection with the present submission; however, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overage.

CONCLUSION

It is believed that all of the claims are patentable and early notification as such is earnestly solicited. If any issues may be resolved by way of telephone, the Examiner is invited to call the undersigned at the telephone number indicated below.

Respectfully submitted,

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Appendix 1

Supporting Experimental Data

As a natural part of the healing process after surgery the body deposits fibrin onto injured tissues. Fibrin acts to seal the injury and allows the deposition of cellular matrix, but may cause tissues that should be separate to adhere to one another and become held together by an adhesion. Adhesions can prevent tissues and organs from moving freely resulting in medical complications requiring treatment.

A series of experiments have been performed to assess the effect of the synthetic lamellar body, LMS-611 on fibrin.

The Effect of the Synthetic Lamellar Body, LMS-611 and Other Phospholipid Mixtures on Fibrin Clot Porosity.

The effect of phosphotidylcholine (PC) (100%), LMS-315 (phosphotidylcholine 65%, sphingomyelin 23% and cholesterol 12%) and LMS-611 (phosphatidylcholine 54%, sphingomyelin 19%, phosphatidylethanolamine 8%, phosphatidylserine 4%, phosphatidylinositol 3% and cholesterol 10%) on the porosity of a fibrin clot were assessed by measuring the volume of saline passing through the clot over a 45 minute period.

By combining fibrinogen and thrombin with the test items (500μl), in a 2ml syringe, an artificial fibrin clot was formed after 60 minutes. A hydrostatic head of saline (0.9% NaCl, 1.5ml) was then added and the flow of saline through the clot collected over a 45 minute period. The saline collected being taken as a measure of the porosity of the clot.

The addition of the synthetic lamellar body, LMS-611 to the fibrin clot was found to increase the porosity of the fibrin clot, as shown by the volume of saline collected after 45 minutes, compared to saline Control, phosphotidylcholine or the phospholipid mixture LMS-315. The latter two test materials were not significantly different from the saline Control (Figure 1).

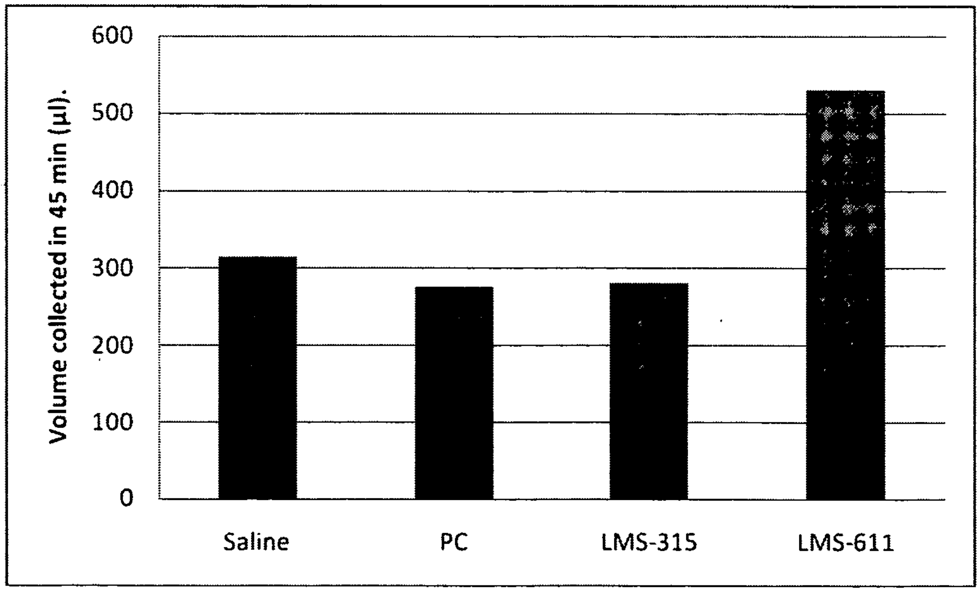

Figure 1. The effect of phosphotidylcholine (PC), LMS-315 and LMS-611 (an example of the claimed composition) on the porosity of a fibrin clot, as measured by the volume of saline penetrating the clot in 45 minutes.

The remaining clots were then visualised using scanning electron microscopy and the clot structures compared. The clot formed in the presence of LMS-611 was found to have a considerably more open structure than those formed in the presence of saline, phosphotidylcholine and LMS-315. The open structure of a fibrin clot formed in the presence of LMS-611 can be seen in the example shown in Figure 2.

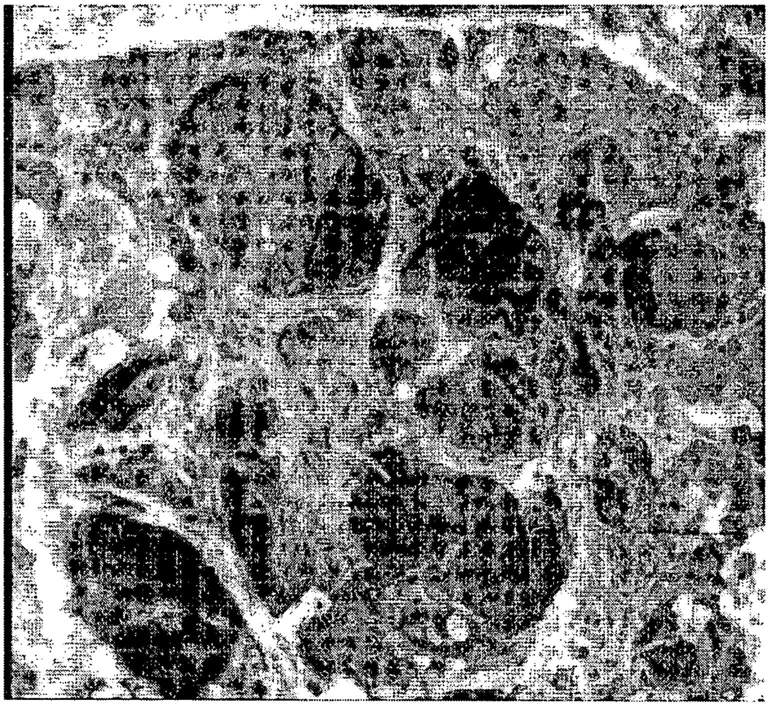

Figure 2. The structure of a fibrin clot treated with LMS-611, as seen using a scanning electron microscope.

As fibrin is the biological gel responsible for adhesions, the administration of the synthetic lamellar body, LMS-611 during surgery will result in permeation and disaggregation of the fibrin and so reduce adhesions.

The Effect of the Synthetic Lamellar Body, LMS-611 and Other Phospholipid Mixtures on Biological Gels *In Vitro.*

Surfactants comprise a mixture of phospholipids and are used to treat infant respiratory distress syndrome. Liposomes are vesicles used as excipients in drug delivery and typically comprise of phospholipids and cholesterol. These phospholipid mixtures act as useful Controls against which to compare the synthetic lamellar body, LMS-611 (phosphatidylcholine, sphingomyelin, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol and cholesterol in amounts as defined previously).

The effect of the surfactants Survanta (25mg/ml) and Curosurf (80mg/ml), and the commercially available, liposomes, L4031 (L-a-phosphatidylcholine, sterylamine and cholesterol) and L4395

(L-a-phosphatidylcholine b-oleoyl-glpalmitoyl, L-a-phosphatidyl-DL-glycerol, dioleoyl and cholesterol) were tested for effect on the adherence of biological gels to an inclined plane. The surfactants had little effect on the adherence of the biological gels to the inclined plane i.e. there was no reduction in the adherence of the biological gel to the inclined plane. Although, Curosurf, on repeated administrations, slowly mobilised DNA which then travelled the distance within the time frame permitted (100% reduction in adherence). The liposomes had a slight effect on the adherence of the gels to the inclined plane. The synthetic lamellar body, LMS-611 (5mg/ml) had an immediate effect, significantly reducing the adherence of **mucus, alginate and DNA** to the inclined plane (Figure 3).

Figure 3. The effect of surfactants, liposomes and LMS-611 on the adherence of different biological gels to an inclined plane.

Methodology: The adherence of biological gels was measured as the resistive flow of the gel down an inclined plane under the influence of gravity (Hubbold, Garner and Chakraborti 2001). Droplets of carboxymethylcellulose (400-800 cps), mucin (5%; from bovine submaxillary glands), DNA (1%; polymeric form from salmon testes) and experimental alginate (manuronic acid) were pipetted in a straight line onto a polystyrene Petri dish, the droplets were tenaciously adherent allowing the dish to be held at a right angle (90°). The droplets were then sprayed with the test article (100µl). The time to travel down the plate was measured. Administration was repeated if the droplet had not travelled the full extent in one minute.